AF/1616

Docket No. 20164 US C038435/0109730 PATENT APPEAL

CERTIFICATE OF MAILING

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Date: February 17, 2004

Sheila Chang
Sheila Chang

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:)

Monika JOHANNSEN) Examiner: Sabiha Naim Qazi

Serial No.: 09/335,022) Group Art Unit: 1616

Filed: June 17, 1999)

For: **PROCESS FOR PRODUCING VITAMIN D_3 AND PREVITAMIN D_3**)

New York, New York
February 17, 2004

APPELLANT'S SECOND BRIEF ON APPEAL

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Arlington, VA 22313-1450

Sir:

This is an appeal from the final rejection of all claims which are pending in the above-identified application.

In accordance with 37 CFR §1.192(a), this brief is being submitted in triplicate, together with the required fee. 37 CFR §1.17(c).

The Notice of Appeal was accorded a filing date of July 24, 2003. A five-month extension of time to file this Second Brief on Appeal is hereby requested. Accordingly,

this Brief is filed timely upon mailing, with an executed Certificate of Mailing, on or before February 24, 2004. 35 USC §21(b); 37 CFR §§1.8, 1.136, and 1.192(a).

Enclosed is a check in the amount of $2,340.00 to cover the fee for filing the Brief ($330.00) and the fee for the extension of time ($2010.00). 37 CFR §1.17. Please charge any fees not otherwise paid by check to Deposit Account No. 02-4467. A duplicate copy of this sheet is enclosed.

IDENTIFICATION OF REAL PARTY IN INTEREST

The real party in interest is DSM NUTRITIONAL PRODUCTS, INC., which is the assignee of the present application and is a corporation organized and existing under, and by virtue of, the laws of the State of Delaware. Ownership of DSM NUTRITIONAL PRODUCTS, INC. lies in DSM N.V., a Dutch corporation.

RELATED APPEALS AND INTERFERENCES

Upon information and belief of the undersigned counsel, Appellant and the assignee are not aware that there are any pending appeals or interferences, which will directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

STATUS OF ALL CLAIMS AND AMENDMENTS

A. Status Prior To Final Rejection

As filed, this Rule 53(d) Continued Prosecution Application ("CPA") contained claims 1-8. In connection with the filing of this application, claims 1 and 2 were amended pursuant to a request to enter a previously unentered amendment from the October 3, 2000 RESPONSE INCLUDING AMENDMENT. Claim 1 was further amended by a

Preliminary Amendment filed concurrently with the CPA to recite that the claimed process is carried out by normal phase chromatography.

In response to the Final Office Action dated September 5, 2001 (Paper No. 17), amendments were presented to the claims and to the specification, but were not entered. [*See* RESPONSE TO OFFICE ACTION UNDER RULE 116 INCLUDING AMENDMENT dated December 5, 2001 ("December 5, 2001 Response") and Paper Nos. 17 and 19]. On March 4, 2002, a COMBINED NOTICE OF APPEAL FROM THE PRIMARY EXAMINER TO THE BOARD OF PATENT APPEALS AND INTERFERENCES & PETITION FOR EXTENSION OF TIME was filed. Subsequently, the APPELLANT'S BRIEF ON APPEAL ("Brief 1") was filed on July 15, 2002.

In response to Brief 1, the Examiner conceded that the rejections were untenable, reopened prosecution and issued an Office Action dated October 21, 2002 (Paper No. 22). In Paper No. 22, the Examiner advised that the amendments presented in the December 5, 2001 Response, including the cancellation of claims 7 and 8, would be entered.

A Response to Office Action was filed on January 21, 2003. No amendments were presented in the Response.

B. Status After Final Rejection

The Examiner issued a Final Rejection on April 21, 2003 (Paper No. 24) and Appellant filed a Notice of Appeal on July 21, 2003, which was received by the PTO on July 24, 2003. No further amendments to the application have been presented subsequent to Paper No. 24.

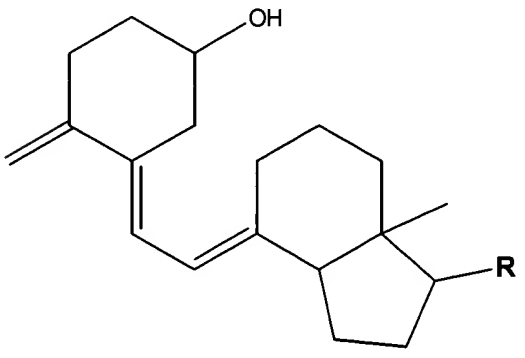
C. Identification Of Claims On Appeal

Claims 1-6 are on appeal and are reproduced in APPENDIX I to this brief.

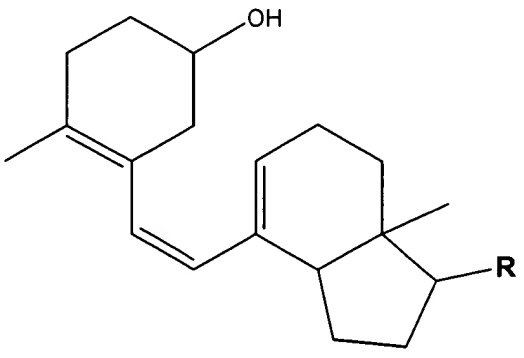
SUMMARY OF THE INVENTION AND THE CLAIMS

The claims on appeal recite a process for the isolation of vitamin D_3 or previtamin D_3 from a mixture containing same. [*See* Claims 1-6]. The D vitamins are biologically active substances that are essential for the regulation of calcium metabolism in higher animals. The various D vitamins differ by the nature of the side chain, and, generally, the most important members of the D vitamins are vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol). The D "previtamins" also are widely distributed in higher animals and plants. The industrial production of the D vitamins is carried out by the conversion of natural precursors, which are related to cholesterol. [Specification, page 1, lines 8-16].

For the convenience of the Examiner and the Board, the structures of vitamin D_3 and previtamin D_3 are set forth below:



Vitamin D_3



Previtamin D_3

Vitamin D_3 is sensitive to light, air, heat and acid. Vitamin D_3 is insoluble in water, minimally soluble in fatty oils and has good solubility in ethanol, chloroform, ether

and acetone. The melting point of vitamin D_3 is from 84 to 87°C. It is known that the D vitamins are soluble in supercritical or subcritical fluids, *e.g.* in supercritical carbon dioxide at temperatures of 40 to 60°C and pressures of 20 to 35 MPa. [Specification, page 1, lines. 17-21].

Conventional processes for the synthesis of vitamin D_3 are based on the irradiation of 7-dehydrocholesterol ("DHC"), which is produced from cholesterol. DHC is converted into previtamin D_3 by irradiation, which is then isomerized to vitamin D_3 by gentle heating. Additional side products, such as lumisterol and tachysterol, also are formed when DHC is irradiated. Thus, the yield of previtamin D_3, and consequently of vitamin D_3, depends essentially on the irradiation conditions. [*Id.*, page 1, lines 21-27].

To reduce unwanted side products that result from the irradiation of DHC, various processes have been used for the purification of the mother liquor after the irradiation step. For example, the tachysterol side product has been converted, using a Diels-Alder reaction, into a tachysterol di-potassium salt adduct, which is subsequently removed. [Specification, page 2, lines 1-4].

Conventional processes for producing vitamin D_3 and previtamin D_3 have a number of disadvantages. For example, the vitamin D_3 yield is limited by the state of equilibrium in the irradiation reaction. In addition, the performance of the Diels-Alder reaction requires additional chemicals and does not give a complete yield of vitamin D_3 or previtamin D_3 based on the crude product. And, purification of the crude product to a crystalline grade also requires additional reactions using chemicals, such as, pyridine and butyryl chloride. This reaction also does not go to completion. In sum, the

conventional processes are inefficient and result in loss of product. [Specification, page 2, lines 5-10].

The present invention provides a process for isolating vitamin D_3 or previtamin D_3 from an isomer mixture of the kind formed, *e.g.*, when using the conventional irradiation process described above while avoiding the drawbacks associated with the conventional isolation processes. To accomplish this, the present invention uses normal phase column chromatography with a mobile phase that contains supercritical carbon dioxide. [*See* Claim 1; and Specification, page 1, lines 3-6; page 2, lines 11-18; and page 2, line 25 – page 3, line 14].

The mobile phase may further include a modifier (claim 2), and the stationary phase may be a silica gel (claim 3). [*Id.*, page 2, lines 16-18]. More particularly, when the stationary phase is silica gel, it is in the form of homogeneously packed, spherical particles having a particle size of about 5 to 25 μm. [*Id.*, Claim 4; and page 4, lines 24-27].

The reaction mixture that is passed through the column may be synthetically produced by irradiation and contain a mixture of vitamin D_3 isomers. [*Id.*, Claim 5; page 2, lines 11-13; and page 2, line 25 to page 3, line 5]. The process may be carried out at temperatures ranging from about 30°C to about 60°C and at pressures ranging from about 7.0 to about 15.0 MPa. [*Id.*, Claim 6; and page 5, lines 5-7].

The process according to the present invention provides significant improvements over the conventional processes described above. Such improvements include avoidance of the Diels-Alder reaction, the ability to recycle byproduct fractions, higher yields, purer product, use of a solvent-free process step, simple separation by

pressure release and problem-free circulation of the eluent. [Specification, page 3, lines 6-14].

STATEMENT OF THE SOLE REJECTION AND ISSUE

The only issue on appeal is whether all claims are unpatentable under 35 USC §103(a) over Higashidate *et al.*, Journal of Chromatography, vol. 515, pp. 295-303 (1990) ("Higashidate") "and" Nakamura *et al.* (DN 120:220844, CAPLUS, abstract of JP 5345898) ("Nakamura"). [*See* Paper No. 24 at 3].

GROUPING OF CLAIMS

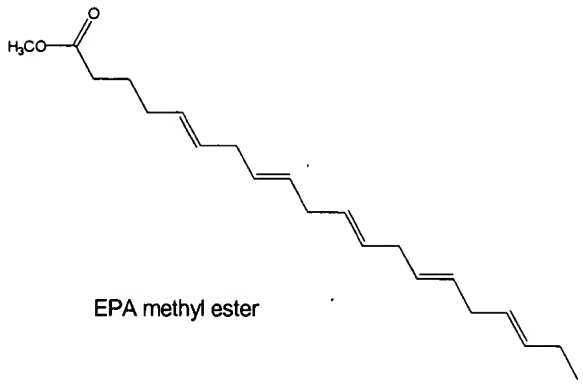
Not all claims stand or fall together.

Arguments are presented below, which demonstrate the patentability of claims 1-3 and 5.

Separate arguments are presented, which demonstrate the separate patentability of claims 4 and 6.

SUMMARY OF THE DISCLOSURES OF THE REFERENCES

Higashidate discloses a method of isolating methyl esters of eicosapentaenoic acid ("EPA") and docosahexaenoic acid ("DHA"). [Higashidate, Page 302]. For the convenience of the Examiner and Board, the structures of these polyunsaturated fatty acids are set forth below:



EPA methyl ester

DHA methyl ester

Higashidate discloses a two-step method for the "enrichment" of EPA and DHA from esterified fish oil. [*See* Abstract; and page 297]. In the first step, EPA and DHA were extracted from an esterified fish oil sample using supercritical fluid extraction ("SFE") with carbon dioxide. [*Id.*, page 297]. When the extraction was complete, supercritical fluid chromatography ("SFC") with carbon dioxide was performed to further purify the EPA and DHA fractions. [*Id.*].

The SFC was performed on a silica gel column coated with silver nitrate. [*Id.*, pages 296, 297]. Higashidate observes that using a silica gel coated with silver nitrate was expected to be advantageous in the SFC process given its known function in liquid chromatography ("LC") applications.

> In LC, it is known that a silica gel column coated with silver nitrate is very suitable for separation of alkenes with *cis* configurations from *n*-alkanes, because *cis*-alkenes form silver chelates that are adsorbed on the stationary phase more strongly than *n*-alkanes. The use of this technique for the concentration of esters of EPA and DHA has been reported. If the compounds behave in the same way in supercritical carbon dioxide mobile phase, then SFC using a silver nitrate-coated silica gel column can enrich EPA and DHA esters efficiently. Such a separation system will have the advantages of both SFE and LC. (citations omitted) [*Id.*, page 296].

Higashidate also observes that direct injection of esterified fish oil was "unsuccessful" because of precipitation problems that led to a decrease in column selectivity.

> However, direct injection of the esterified fish oil was unsuccessful in this fractionation, because constituents of the esterified fish oil insoluble in supercritical carbon dioxide precipitated and covered the stationary phase, resulting in a decrease in the selectivity of the column. [*Id.*, page 297].

Higashidate concludes that the disclosed method results in "enrichment" of the amount of EPA and DHA methyl esters in the column fractions, to *e.g.*, 93% and 82%, respectively. [*Id.*, pages 298 and 302 (Table I)].

Nakamura is an abstract of JP 5345898.[1/] Because of its brevity, we reproduce Nakamura in its entirety below:

> The process using no aliph. hydrocarbons comprises dissolving raw material oil in liquefied CO_2 and passing the liq. under supercrit. conditions through a packed column. Placing 10 g crude Macadamia nut oil (APHA color 100) in a column packed with 10 g silica gel and passing liquefied CO_2 through the column at 50 atm gave a liq., which after CO_2 evapn. yielded 8.9 g oil with APHA color 5 and no malodor.

SUMMARY OF THE POSITIONS TAKEN BY THE EXAMINER IN THE FINAL OFFICE ACTION

In the final Office Action, the Examiner rejected claims 1-6 solely under §103(a) as unpatentable over Higashidate "and" Nakamura "for the same reasons as set forth in our previous Office Action [Paper No. 22]."[2/] [Paper No. 24 at 3]. The Examiner

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1/ We note that the rejection limits its consideration of Nakamura solely to the disclosure contained in the Nakamura abstract made of record by the Examiner. Accordingly, all references to Nakamura herein are to the abstract of record.

2/ It is unclear from the record whether the Examiner intends this rejection to be a combination rejection, *i.e.*, Higashidate in view of Nakamura or two separate rejections. The previous Office Action (Paper No. 22 at 4) is similarly unclear. As developed in more detail below, this ambiguity

explained that the cited documents "teach" the use of silica gel and supercritical carbon dioxide for separation and isolation of "components." [*Id.*]

> Prior art cited teach separation and isolation of components on silica gel as stationary phase and super critical carbon dioxide as mobile phase, which embraces Applicant's claimed invention. [*Id.*].

In making the rejection(s), the Examiner asserted that Higashidate "teaches" the enrichment of EPA and DHA in a two-step process utilizing supercritical fluid extraction coupled with supercritical fluid chromatography. [*Id.*, pages 3-4].

> Higashidate teaches enrichment of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) I [sic] from 12% to 93% and from 13% to 82% respectively. Methyl esters of EPA and DHA in esterfi[ed] fish oil were extracted by supercritical fluid extraction with carbon dioxide and directly introduced into [sic] silica gel column coated with silver nitrate. Changing the pressure of the column outlet [sic] then performed supercritical fluid chromatography with carbon dioxide. Reducing the pressure fractionated the EPA and DHA methyl esters thus separated. [*Id.*].

The Examiner summarized Nakamura – in one sentence – as "teaching" the use of a silica gel in a supercritical carbon dioxide separation technique. [*Id.* at 3].

> Nakamura teaches use of silica gel column chromatography in supercritical carbon dioxide separation technique. [*Id.*].

The Examiner acknowledged that "the reference" does not disclose separating vitamin D_3 or previtamin D_3. [*Id.* at 4]. The Examiner, however, concluded that separating vitamin D_3 or previtamin D_3 using the claimed process would have been obvious because the "technique is now commonly used." [*Id.*].

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is reason enough to reverse the rejection. If the rejection is not withdrawn, the Examiner is respectfully requested to clarify the rejection(s) in her Answer.

> Instant claims differ from the reference in claiming isolation of specific compounds vitamin D_3 and previtamin D_3 from the mixture whereas prior art teaches methods for separation of various compounds by supercritical carbon dioxide as instantly claimed. This technique ***is now*** commonly used. (emphasis added) [*Id.*].

The Examiner further explained this conclusion by observing that it would have been obvious "to be motivated" to carry out the claimed invention because "nothing unobvious is seen" in separating vitamin D_3 or previtamin D_3 using supercritical carbon dioxide and silica gel. [*Id.*].

> It would have been ***obvious*** to one skilled in the art ***to be motivated*** to separate components of the mixture by using supercritical carbon dioxide as mobile phase and silica gel as stationary phase. Size of the silica gel particle and pressure ***are selected*** depending on the type of compounds intended to isolate. One skilled in the art who ***is*** familiar with the separation techniques would ***know*** to use the size of the particles and other adjustments in order to enhance the yield of the process.
>
> Since the extraction with super critical carbon dioxide and passing the liquid under supercritical conditions through a packed column is taught by the prior art, there is [sic] ***nothing unobvious is seen*** to separate vitamin D_3 and previtamin D_3 from the mixture by using supercritical carbon dioxide and silica gel for the isolation of the said compounds.
>
> In light of the foregoing discussion, the Examiner's ultimate legal conclusion is that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC §103(a). (emphasis added) [*Id.* at 4-5].

THE LEGAL STANDARD

To reject a claim under 35 USC §103, an examiner must show an unrebutted *prima facie* case of obviousness. *In re Deuel*, 34 USPQ2d 1210, 1214 (Fed. Cir. 1995). Obviousness must be based upon facts. *Ex parte Saceman*, 27 USPQ2d 1472, 1474

(BPAI 1993). When a conclusion of obviousness is not based on facts, it cannot stand. *Ex parte Porter*, 25 USPQ2d 1144, 1147 (BPAI 1992).

In combining references, the suggestion and motivation to make the combination must be based on "actual evidence" that must be "clear and particular." *In re Dembiczak*, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999) *abrogated on other grounds by In re Gartside*, 53 USPQ2d 1769 (Fed. Cir. 2000). Moreover, when the PTO asserts that there is an explicit or implicit teaching or suggestion in the prior art, it must indicate where such a teaching or suggestion appears in the references. *In re Rijckaert*, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) *citing In re Yates*, 211 USPQ 1149 (CCPA 1981).

In the absence of a proper *prima facie* case of obviousness, an applicant who complies with the other statutory requirements is entitled to a patent. *In re Glaug*, 62 USPQ2d 1151, 1152 (Fed. Cir. 2002); and *In re Oetiker*, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). On appeal to the Board, an applicant can overcome a rejection by showing insufficient evidence of *prima facie* obviousness. *In re Oetiker*, 24 USPQ2d at 1444.

SUMMARY OF THE ARGUMENT

The Examiner has failed to meet her burden of setting forth a *prima facie* case of obviousness. The sole rejection under appeal is legally and factually deficient, and, therefore, cannot stand.

The rejection is legally deficient because the Examiner applied the wrong standard and performed the obvious analysis from the vantage point of when the rejection was written, not just prior to when the invention was made, as required by statute and binding authority. In doing so, the Examiner impermissibly shifted the burden to the Appellant to demonstrate that the claimed invention was unobvious.

The rejection is also ambiguous - it does not clearly set forth whether it is a rejection based on the combination of Higashidate in view of Nakamura or two separate rejections based on Higashidate and Nakamura individually. If the rejection is based on the combination of Higashidate in view of Nakamura, it is further legally deficient because it fails to identify evidence from the cited documents - or any other source - that provides motivation or suggestion to combine the documents in the manner proposed by the Examiner. Nor does the rejection identify any evidence that the proposed combination would provide a reasonable expectation of carrying out a successful isolation of vitamin D_3 or previtamin D_3 as claimed. And, even if there is a motivation to combine the documents, which there is not, the proposed combination would require impermissibly modifying Higashidate in a manner contrary to its disclosure.

The rejection is also factually deficient. Although the Examiner acknowledges that neither cited document discloses a process for the isolation of vitamin D_3 or previtamin D_3, she nonetheless presses the rejection without the required disclosure in the cited documents of the missing claim element. Thus, Higashidate and Nakamura, alone or in combination, do not disclose or suggest the claimed process as a whole.

The Examiner never even addressed, much less demonstrated, that dependent claim 6 would have been obvious, and the Examiner's summary "within the skill" argument is insufficient to render claim 4 obvious.

ARGUMENT

POINT I
THE EXAMINER APPLIED THE WRONG STANDARD, FAILED TO FOLLOW PTO PROCEDURE AND FEDERAL CIRCUIT PRECEDENT AND IMPROPERLY PLACED THE INITIAL BURDEN ON THE APPLICANT TO DEMONSTRATE NON-OBVIOUSNESS

a. "Obvious ... to Be Motivated" Is Not The Standard

The first error is that the Examiner failed to provide any authority to support the unheralded standard she used to reject claims 1-6. In making the rejection under §103, the Examiner asserted that "[i]t would have been obvious ... to be motivated to separate components of the mixture by using supercritical carbon dioxide as mobile phase and silica gel as stationary phase." [Paper No. 24 at 4]. Clearly, the Examiner's analysis was focused on whether it would have been "obvious ... to be motivated" to carry out the claimed process.

"Obvious ... to be motivated," however, is not the standard under §103(a). The statute requires that the Examiner determine whether the subject matter of the claimed invention, as a whole, would have been obvious in view of the prior art - not whether a "motivation" would have been obvious.

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made. 35 USC §103(a).

The Examiner acknowledged that neither Higashidate nor Nakamura disclose separating vitamin D_3 and previtamin D_3. [Paper No. 24 at 4]. But, the Examiner did not

identify any disclosure in Higashidate or Nakamura that would have motivated or suggested replacing EPA (Higashidate), DHA (Higashidate) and macadamia nut oil (Nakamura) with vitamin D_3 or previtamin D_3. Nor did the Examiner consider the structural differences between the vitamin D_3 and previtamin D_3 recited in the claimed process and EPA, DHA and macadamia nut oil disclosed in the cited documents or how those differences would have impacted the proposed interchangeability of the respective components.

Rather, the Examiner focused on whether "it would have been obvious ... to be motivated" to separate any component of any mixture using supercritical carbon dioxide as a mobile phase and silica gel as the stationary phase. [Paper No. 24 at 4]. In doing so, the Examiner applied a new standard of obviousness that avoids any analysis of the acknowledged differences between the claimed invention and the cited documents and whether the claimed invention as a whole would have been obvious.

At bottom, the Examiner's "obvious ... to be motivated" standard is nothing more than a conclusion that it would have been obvious-to-try to separate vitamin D_3 and previtamin D_3 because the cited documents disclose separation of EPA, DHA and macadamia nut oil. As is well settled, "obvious-to-try," no matter how it is disguised in a rejection, is not the standard under §103. *In re Goodwin*, 198 USPQ 1, 3 (CCPA 1978) (CCPA rejected as an impermissible obvious to try standard the Board's conclusion that a prior art disclosure of carbon monofluoride lubricants, which are stable in oxidizing atmospheres at temperatures up to 800°C would have suggested the use of those compounds in a glass manufacturing process at temperatures in excess of 800°C); *In re Antoine*, 195 USPQ 6, 8 (CCPA 1977) ("The PTO and the minority appear to argue that

it would always be *obvious* for one of ordinary skill in the art *to try* varying *every* parameter of a system in order to optimize the effectiveness of the system even if there is no evidence in the record that the prior art recognized that particular parameter affected the result. As we have said many times, obvious to try is not the standard of 35 USC §103.") (emphasis in original) (internal citations omitted); and *In re Tomlinson*, 150 USPQ 623, 626 (CCPA 1966) (The CCPA rejected as an impermissible obvious-to-try standard the Examiner's and Board's conclusion that "'it would have been obvious for a skilled chemist to try to stabilize polypropylene with a known stabilizer for polyethylene;' and that it would be 'routine experimentation for a skilled chemist to attempt to stabilize polypropylene against the deteriorative effect of light ...'").

Indeed, the present rejection is far worse than the one in *Goodwin* wherein the gap the Examiner and Board tried to bridge was the absence of a disclosure to use a higher temperature from the temperatures that were disclosed. Here, the Examiner admits that neither cited document discloses separating vitamins, let alone vitamin D_3 or previtamin D_3.

Similarly, the situation here is far worse than in *Antoine* and *Tomlinson* where the Examiner and Board argued that the respective disclosures in the prior art were sufficient for one to arrive at the claimed invention (*i.e.*, by assuming that increasing tank volume to surface area increased efficiency was disclosed in the prior art and that working out an optimal efficiency would have been obvious (*Antoine*) or assuming that because polyethylene and polypropylene were structurally similar it would have been obvious to determine stabilizers for polypropylene given the prior art disclosure of stabilizers for polyethylene (*Tomlinson*)). Here, the Examiner identifies no disclosure

from either Higashidate or Nakamura that suggests that vitamin D_3 and previtamin D_3 are structurally similar to the disclosed EPA and DHA (Higashidate) or macadamia nut oil (Nakamura). Nor does the Examiner identify any disclosure or suggestion that the separation processes of Higashidate and Nakamura would have even worked with compounds having the structures of vitamin D_3 and previtamin D_3.

At bottom, use of the "obvious ... to be motivated" standard by the Examiner ignored long standing precedent to the contrary and impermissibly relied on the Appellant's specification as a blueprint to provide the motivation to isolate vitamin D_3 or previtamin D_3 that was lacking from Higashidate and Nakamura. But, as is well settled, the kind of hindsight analysis used by the Examiner to jump from polyunsaturated fatty acids (DHA and EPA) or an oil (macadamia nut oil) to a vitamin (D_3 or previtamin D_3) is not permitted. Thus, because the Examiner applied an "obvious to be motivated" standard akin to an obvious-to-try standard and engaged in hindsight reconstruction using the Appellant's specification, the rejection should be reversed.

b. "Nothing Unobvious" Is Not The Standard

The Examiner also relied on a "nothing unobvious" standard to reject claims 1-6. [Paper No. 24 at 4]. The Examiner apparently concluded that because Higashidate discloses separating EPA and DHA using SFC with supercritical carbon dioxide and *e.g.*, claim 1 recites a process that comprises using a normal phase column chromatographic technique with supercritical carbon dioxide that there is "nothing unobvious" (1) to replace the starting fish oil extract of Higashidate with a mixture containing vitamin D_3 or previtamin D_3 as claimed; (2) to replace the silver nitrate coated

silica gel of Higashidate with the silica gel of Nakamura; and (3) to replace the isolated EPA and DHA methyl esters with vitamin D_3 or previtamin D_3.

Again, by hiding behind the veil of a new obviousness standard, the Examiner avoided any sort of factual analysis to support her "ultimate legal conclusion." [*See* Paper No. 24 at 5]. "Nothing unobvious" is not a substitute for explaining why the acknowledged differences between Higashidate and Nakamura and the rejected claims would have been obvious. *Antoine*, 195 USPQ at 8 ("The controlling question is simply whether the differences ... between the prior art and appellant's invention as a whole ... would have been obvious."). "Nothing unobvious" is not a substitute for identifying evidence in the cited documents for making the proposed substitutions. *Dembiczak*, 50 USPQ2d at 1617. And, "nothing unobvious" does not absolve the Examiner of her burden to explain with evidence from the cited documents and/or with technical reasoning the bases for her "ultimate legal conclusion" (*see* Paper No. 24 at 5). *See Saceman*, 27 USPQ2d at 1474; and *Porter*, 25 USPQ2d at 1147.

Moreover, reliance on a "nothing unobvious" standard impermissibly shifts the burden to the Appellant to come forth with evidence of nonobviousness in the absence of a *prima facie* showing of obvious. Appellant has no such burden. *In re Piasecki*, 223 USPQ 785, 788 (Fed. Cir. 1984) ("As adapted to *ex parte* procedure, *Graham* is interpreted as continuing to place the 'burden of proof on the Patent Office which requires it to produce the factual basis for its rejection of an application under sections 102 and 103.'"); and MPEP §706.02(j) at 700-45 (8th Ed. rev. Feb. 2003) ("The initial burden is on the examiner to provide some suggestion of the desirability of doing what the inventor has done."); and MPEP §2142 at 2100-123 ("If the Examiner does not

produce a *prima facie* case, the applicant is under no obligation to submit evidence of nonobviousness.").

Accordingly, because the Examiner relied on a non-statutory standard, failed to engage in the required factual analysis and impermissibly shifted the burden to the Appellant to present evidence of nonobviousness, the rejection is legally deficient and should be reversed for these reasons as well.

c. "Now" Is the Wrong Time Point To Conduct The Obviousness Analysis

Another error is that the rejection carries out its limited analysis from the vantage point of one skilled in the art *circa* April 2003, namely, at the time the rejection was made, not just prior to the date the invention was made, as required by the statute, binding Federal Circuit precedent, and the PTO's own rules. *See* 35 USC §103(a); *In re Fine*, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988) *quoting Panduit Corp. v. Dennison Mfg. Co.*, 1 USPQ2d 1593, 1595-96 (Fed. Cir. 1987) ("To reach a proper conclusion under §103, the decision maker ***must*** step backward in time and into the shoes worn by [a person having ordinary skill in the art] when the invention was unknown and just before it was made.") (emphasis added); and MPEP §2142 at 2100-123 ("To reach a proper determination under 35 USC §103, the examiner ***must*** step backward in time and into the shoes worn by the hypothetical 'person of ordinary skill in the art' when the invention was unknown and just before it was made.") (emphasis added).

The analysis carried out by the Examiner was conducted based on the knowledge of the skilled artisan at the time the rejection was made. The Examiner stated that "[t]his technique ***is now*** commonly used." [Paper No. 24 at 4]. The Examiner also stated that "[o]ne skilled in the art who ***is familiar*** with the separation

techniques ***would know*** how to ...." [*Id.*]. The Examiner also stated that the "[s]ize of the silica gel particle and pressure ***are*** selected ..." And, the Examiner stated that "... nothing unobvious ***is*** seen to separate vitamin D_3 and previtamin D_3 ...." [*Id.*].

The Examiner's analysis unmistakably uses verb forms of the present tense - "is," "are" and "know" – and is punctuated by the use of the term "now." The record is clear - the Examiner analyzed the claims from the vantage point of when she wrote the rejection. This is error. *See Fine*, 5 USPQ2d at 1598. What one skilled in the art "would know" today, what one "is familiar" with today and what "is now commonly used" is irrelevant to a determination under §103. What the Examiner was required to do, but did not do, was to go back in time to just before the invention was made, and consider what one skilled in the art "would have known" based on Higashidate and Nakamura. Because the Examiner failed to conduct the obviousness analysis from the vantage point of one skilled in the art just prior to the time the invention was made, the rejection should be reversed for this reason as well.

d. The Rejection Is Ambiguous

Another error is that the rejection is unclear whether the Examiner intended a single rejection based on the ***combination*** of Higashidate in view of Nakamura or two separate rejections based on Higashidate and Nakamura ***individually***. The Appellant is thus left to guess, which of the two possible rejections was intended by the Examiner. This violates clear Federal Circuit precedent and the PTO's own internal rules requiring that rejections be made "fully and clearly."

The rejection begins with a statement that the claims are rejected over Higashidate "and" Nakamura. [Paper No. 24 at 3]. This suggests that the Examiner

intended to make two separate rejections. In the rest of the Office Action, however, Nakamura is specifically discussed in only one sentence:

> Nakamura teaches use of silica gel column chromatography in supercritical carbon dioxide separation technique. [*Id.*].

In the paragraph following the Nakamura summary, the Examiner asserted that the Higashidate silicon gel column is "coated with silver nitrate." [*Id.*]. Although nowhere is it explicitly set forth in the rejection, given the single sentence description of Nakamura, the Examiner may have intended to replace the silver nitrate coated silica gel of Higashidate with the silica gel of Nakamura. We simply cannot tell.

The PTO's own internal rules require that an Examiner "fully and clearly" state the ground of each rejection. MPEP §707.07(d) at 700-112-13 ("Where a claim is refused for any reason relating to the merits thereof it should be 'rejected' and the ground of rejection ***fully and clearly stated*** ....") (emphasis added). Federal Circuit demands it. *In re Lee*, 61 USPQ2d 1430, 1432-33 (Fed. Cir. 2002) ("For judicial review to be meaningfully achieved within these strictures, the agency tribunal must present a ***full and reasoned explanation*** of its findings and grounds thereof, as supported by the agency record, and explain its application of the law to the found facts.") (emphasis added). And, the Board requires it of the examining corps. *Ex parte Suares*, 2003 WL 23013248, *2 (BPAI 2003) (unpublished) ("... in order for the Board to make a meaningful review of the rejection on appeal, [sic] examiner likewise must present a ***full and reasoned explanation*** in support of the final rejection.") (emphasis added).

Where, as here, the rejection is ambiguous as to which of two possible rejections are made, the rejection is not "fully and clearly stated" as demanded by the PTO's own

rules. Where, as here, the Appellant is left to guess at which of two possible rejections is presented, the Office Action does not contain a "full and reasoned explanation" of the rejection as required by the Federal Circuit and the Board. And, here, just as in *Lee* and *Suares*, the rejection cannot stand and should be reversed.

POINT II

THE REJECTION PROVIDES NO EVIDENCE OF A MOTIVATION TO COMBINE HIGASHIDATE AND NAKAMURA IN THE MANNER APPARENTLY SUGGESTED NOR DOES THE REJECTION IDENTIFY WHERE A REASONABLE EXPECTATION OF SUCCESS IS FOUND IN THE CITED DOCUMENTS

If the rejection is intended to be a combination of Higashidate in view of Nakamura, the Examiner committed additional errors with respect to the attempted combination. Specifically, another error is that the rejection fails to identify any suggestion or motivation to combine Higashidate and Nakamura.

As is well settled, however, a *prima facie* case of obviousness requires that the rejection describe with specificity ***why*** one skilled in the art would have combined the references to arrive at the claimed invention. *Dembiczak*, 50 USPQ2d at 1617. ("Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of *the requirement for a showing of the teaching or motivation to combine prior art references.*") (emphasis added). The factual inquiry into whether to combine references must be "thorough and searching." *McGinley v. Franklin Sports, Inc.*, 60 USPQ2d 1001, 1008 (Fed. Cir. 2001). And, the teaching, motivation, or suggestion to combine must come from "***objective evidence of record***." *In re Lee*, 61 USPQ2d at 1433 (emphasis added). As explained

below, no such explanation or showing for the apparent combination is found in the rejection.

The rejection is not clear on how – if at all – it intends that Higashidate be combined with Nakamura.[3/] As best we can tell, the Examiner proposed to substitute the stationary phase of Nakamura – a silica gel column – for the stationary phase of Higashidate – a ***silver nitrate*** coated silica gel column in the Higashidate process. [Paper No. 24 at 3].

Whatever the intended combination, the rejection fails to identify any evidence from either Higashidate or Nakamura that would have suggested or motivated one to combine the documents. Rather, the Examiner relied on conclusory statements that "[t]his technique is now commonly used;" that "one who is familiar with the separation techniques would know to use the particles ... to enhance the yield ...;" and that "nothing unobvious is seen to separate vitamin D_3 and previtamin D_3 ...." [*Id.* at 4]. Again, the Examiner's analysis misses the mark. Focusing on whether one "is familiar" with a separation technique and knows how to enhance yields falls short of the kind of evidence required to combine documents demanded by *Lee*. Focusing on whether "nothing unobvious is seen" also falls short of the evidence required by *Lee*. And, focusing on whether the technique "is now commonly used" avoids consideration and analysis of evidence from the cited documents and knowledge at the time the invention was made.

Notwithstanding the lack of any evidence in the rejection for the proposed combination, all of the arguments advanced by the Examiner are temporally barred by

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3/ For the reasons set forth in Section (I)(d) of this Appeal Brief, this ambiguity is enough to require reversal of the rejection. *See Lee*, 61 USPQ2d at 1432-33; *Suares*, 2003 WL at *2; and MPEP §707.07(d).

the statute. As set forth above, the motivation to combine must come from the cited documents themselves or the knowledge of those skilled in the art just prior to the date that the invention was made. Put another way, the motivation/suggestion to combine Higashidate and Nakamura must have occurred to one skilled in the art just prior to the time the invention was made - not at the time the rejection was written. *In re Fritch*, 23 USPQ2d 1780, 1783-84 (Fed. Cir. 1992) ("The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious ***unless the prior art suggested the*** desirability of the ***modification***.") (emphasis added). Focusing on whether the technique "is now commonly used" avoids having to present evidence of what one skilled in the art would have known about the technique at the time the invention was made. Focusing on whether one "is familiar with the separation techniques" avoids an analysis of what was known at the time the invention was made. And, focusing on whether "nothing unobvious is seen" avoids a determination of what one skilled in the art would have "seen." Because the rejection provided no evidence from Higashidate or Nakamura to explain why they should be combined, the rejection is legally insufficient and should be reversed.

Another error is that the rejection is devoid of any indication of where in Higashidate and Nakamura a reasonable expectation of success would have been found that the suggested combination would work for separating vitamin D_3 or previtamin D_3. But that too was part of the Examiner's *prima facie* case. *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988) ("The consistent criterion for determination of obviousness is whether the prior art would have suggested ... that this process should be carried out and would have a reasonable likelihood of success,

viewed in light of the prior art. Both the suggestion and that expectation of success ***must*** be founded in the prior art, not in the applicant's disclosure.") (emphasis added) (internal citations omitted).

Just as the Examiner failed to identify any suggestion or motivation from the prior art - or anywhere else - for the proposed combination, so too did she fail to identify the basis for her apparent assumption that the proposed combination of Higashidate and Nakamura would have provided a reasonable expectation of successfully isolating vitamin D_3 or previtamin D_3. The rejection is simply devoid of any description or explanation of a nexus between separating EPA, DHA and macadamia nut oil and the claimed process for isolating vitamin D_3 or previtamin D_3. In the absence of any explanation why the proposed combination would have a reasonable expectation of success, the rejection is legally flawed, and should be reversed for this reason as well.

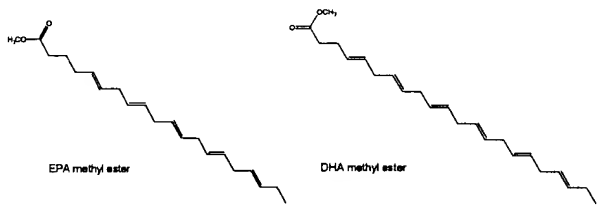
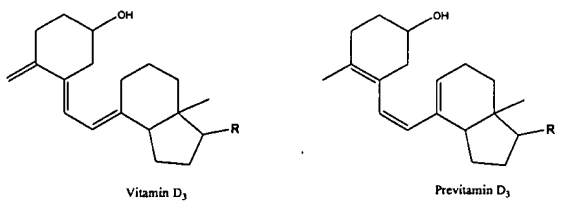
Another error is that the rejection is factually deficient to support the proposed combination. As is well settled, the Examiner is required to demonstrate ***where*** in Higashidate and Nakamura there is a suggestion that would have "strongly motivated" one to modify the disclosures to arrive at the claimed invention. *Ex parte Grasselli*, 231 USPQ 393, 394 (Bd. App. 1986). The type of motivation that would have "***impelled***" one to do so (*Ex parte Levengood*, 28 USPQ2d 1300, 1301-02 (BPAI 1993)), and the type of suggestion that the changes "***should***" be made. *Ex parte Markowitz*, 143 USPQ 303, 305 (Bd. App. 1964).

The Examiner, however, has not identified ***any*** suggestion, reason, or other motivation, including suggestion of desirability, for ***why*** one would have been led to ignore the two-step process for isolating methyl esters of EPA and DHA to arrive at a

single step process for the isolation of vitamin D_3 or previtamin D_3 from a mixture as claimed.

Higashidate discloses the isolation of EPA and DHA methyl esters from esterified fish oil. [Higashidate, page 296-297]. Higashidate is specific as to the separation processes used to isolate EPA and DHA. Indeed, even the stationary phase - containing a silver nitrate coated silica gel - is optimized for separating EPA and DHA. Higashidate discloses that the silver nitrate coated silica gel allows for the efficient separation of alkenes with *cis* configurations from *n*-alkanes because *cis* alkenes form silver chelates that are adsorbed onto the stationary phase more strongly than *n*-alkanes. [*Id.*, page 296].

The claimed invention, however, is a process for the isolation of vitamin D_3 or previtamin D_3 from a mixture containing vitamin D_3 or previtamin D_3. As shown in the table below, vitamin D_3 and previtamin D_3 are structurally different than the EPA and DHA methyl esters isolated by Higashidate:

Higashidate	**D_3 Compounds**
	

Higashidate does not disclose the isolation of any substance other than methyl esters of EPA and DHA, and is absolutely silent as to the isolation of any vitamin, much

less vitamin D_3 or previtamin D_3. This is a factual gap the Examiner acknowledges, but fails to fill:

> Instant claims differ from the reference in claiming isolation of specific compounds vitamin D_3, and previtamin D_3, from the mixture ...." [Paper No. 24 at 4].

While the Examiner apparently recognizes the very specific disclosure of Higashidate, the rejection attempts to extrapolate a general method of isolation from this very limited disclosure.

As appears, the Examiner relies on Nakamura to show isolation of compounds by chromatography with a supercritical carbon dioxide mobile phase and a silica gel stationary phase. [*Id.* at 3]. Nakamura, however, does not disclose the separation of a compound. Nakamura discloses the purification of an oil, specifically macadamia nut oil, using a silica gel column and a "liquefied CO_2" mobile phase. Nakamura does not disclose or suggest the separation of any compound, much less vitamin D_3 or previtamin D_3.

At bottom, neither Higashidate nor Nakamura disclose or suggest the isolation of vitamin D_3 or previtamin D_3 from a mixture. The rejection substituted conjecture and unsupported observations about the current state-of-the-art for the required factual analysis based on the record. *See Ex parte Humphreys*, 24 USPQ 2d 1255, 1262 (BPAI 1992) ("The Examiner's rejection is not specific as to how one of ordinary skill in the art would have found it (the claimed invention) obvious ...."). Thus, the rejection is factually deficient to support a rejection under §103 based on Higashidate and Nakamura, whether taken alone or in combination. For this reason also the rejection should be reversed.

We also observe that just because it may be theoretically possible to arrive at the claimed invention by picking and choosing elements from the prior art, that is not a proper basis for a rejection under §103. *See In re Fritch*, 23 USPQ2d 1780, 1783-1784 (Fed. Cir. 1992) ("The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification."). Thus, what the Examiner was required to do - but did not do - was to provide some motivation from Higashidate or Nakamura that would have suggested the desirability of replacing the silver nitrate coated silica gel of Higashidate with the silica gel of Nakamura. And, what the Examiner was required to do - but did not do - was to identify some motivation from Higashidate or Nakamura that vitamin D_3 or previtamin D_3 could have been isolated with the proposed process. Because the rejection is devoid of any of this kind of evidence, it should be reversed for this reason as well.

POINT III

THE APPARENT COMBINATION OF HIGASHIDATE AND NAKAMURA WOULD RESULT IN A SUBSTANTIAL REDESIGN OF HIGASHIDATE AND AN IMPERMISSIBLE CHANGE IN THE BASIC PRINCIPLES UNDERLYING THE HIGASHIDATE PROCESS

Yet another error is that the Examiner overlooked a fundamental difference between Higashidate and Nakamura. Namely, Higashidate features the use of a silver nitrate coated silica gel column to more efficiently separate EPA and DHA.

> In LC, it is known that a silica gel column coated with silver nitrate is very suitable for separation of alkenes with *cis* configurations from *n*-alkanes, because *cis*-alkenes form silver chelates that are adsorbed on the stationary phase more strongly than *n*-alkanes. The use of this technique for the concentration of esters of EPA and DHA has been

> reported. If the compounds behave in the same way in supercritical carbon dioxide mobile phase, then SFC using a silver nitrate-coated silica gel column can enrich EPA and DHA esters efficiently. Such a separation system will have the advantages of both SFE and LC. [Higashidate, page 296].

To do what the Examiner apparently proposes – replace the silver nitrate-coated silica gel of Higashidate with the silica gel of Nakamura – would alter the fundamental principle underlying the Higashidate process, *i.e.*, to efficiently isolate EPA and DHA methyl esters by forming silver chelates "that are adsorbed on the stationary phase more strongly than *n*-alkanes." [*Id.*]. This kind of reconstruction of a reference is expressly prohibited. *See e.g. In re* Gordon, 221 USPQ 1125, 1127 (Fed. Cir. 1984) ("Indeed, if the French apparatus were turned upside down, it would be rendered inoperable for its intended purpose."); *In re Ratti*, 123 USPQ 349, 352 (CCPA 1959) ("This suggested combination of references would require a substantial reconstruction and redesign of the elements shown in Chinnery *et al.* as well as a change in the basic principles under which the Chinnery *et al.* construction was designed to operate."); and *Ex parte Cavigelli*, 2003 WL 23174998, *5 (BPAI 2003) (unpublished) (Board reversed an examiner's §103 rejection that would have required substituting a ferromagnetic coil for a non-ferrous coil in an apparatus for monitoring leakage currents between an insulator and ground.).

Thus, to substitute the Nakamura silica gel for the silver nitrate coated gel in Higashidate, as the Examiner apparently suggests, would change the basic principles under which the Higashidate process was designed to function, namely to efficiently

separate methyl esters of EPA and DHA. But this it cannot do. Accordingly, for this reason, as well, the rejection should be reversed.

POINT IV

HIGASHIDATE AND NAKAMURA, ALONE OR IN COMBINATION, DO NOT DISCLOSE THE CLAIMED INVENTION

Notwithstanding the foregoing, whether alone or in combination, Higashidate and Nakamura, fail to disclose or suggest each and every element of the claimed invention. The claimed invention recites separating "vitamin D_3 or previtamin D_3" from a mixture. *See e.g.*, claim 1. As discussed above, neither Higashidate nor Nakamura disclose or suggest the separation of vitamin D_3 or previtamin D_3 in any manner.

Higashidate discloses a method for enriching the concentration of two polyunsaturated fatty acids (PUFAs), EPA and DHA, in an esterified fish oil. [Higashidate, pages 296-297]. PUFAs are fatty acids with multiple carbon-carbon double bonds (*See* above). By contrast, vitamin D_3 and previtamin D_3 are not PUFAs and the Examiner has presented no evidence as to why one would consider such compounds to be structurally similar. (*See* above.)

However, Higashidate specifically notes the limitations of the disclosed method:

> The extraction vessel was used in order to introduce only constituents of the fish oil that are soluble in supercritical carbon dioxide into the separation column. This was successful in the fractionation of EPA and DHA methyl esters. However, direct injection of the esterified fish oil was unsuccessful in this fractionation, because constituents of the esterified fish oil insoluble in supercritical carbon dioxide precipitated and covered the stationary phase, resulting in the decrease selectivity of the column. (Page 297).

And, the Higashidate process is specifically optimized for separating alkenes with *cis* configuration from *n*-alkanes. [*Id.*, page 296].

> In LC, it is known that a silica gel column coated with silver nitrate is very suitable for separation of alkenes with *cis* configurations from *n*-alkanes, because *cis*-alkenes form silver chelates that are adsorbed on the stationary phase more strongly than *n*-alkanes. [*Id*].

Thus, the disclosure of Higashidate is limited to separating polyunsaturated fatty acids in general, and methyl esters of EPA and DHA specifically, from a fraction of esterified fish oil that is soluble in supercritical carbon dioxide. The Examiner has not made of record any relevant evidence that Higashidate discloses or suggests separating vitamin D_3 or previtamin D_3 from a mixture containing vitamin D_3 or previtamin D_3.

Nakamura is even less helpful to the Examiner. Nakamura discloses the isolation of an oil from a starting sample of macadamia nut oil using a silica gel column and liquefied carbon dioxide at a pressure of 50 atm. The Examiner identified no disclosure in Nakamura even remotely related to vitamin D_3 or previtamin D_3. Nor did the Examiner even attempt to explain how separation of some component oil from macadamia nut oil would have been viewed as relevant to separating vitamin D_3 or previtamin D_3 from a mixture.

Thus, whether alone or in combination, Higashidate and Nakamura do not disclose or even suggest the claimed process for the isolation of vitamin D_3 or previtamin D_3. For this reason, as well, the rejection should be reversed.

POINT V

THE EXAMINER NEVER ADDRESSED, MUCH LESS DEMONSTRATED THAT DEPENDENT CLAIM 6 WOULD HAVE BEEN OBVIOUS, AND THE EXAMINER'S SUMMARY "WITHIN THE SKILL" ARGUMENT IS INSUFFICIENT TO RENDER CLAIM 4 OBVIOUS

Another error is that the Examiner completely ignored claim 6 and thus failed to engage in the mandatory analysis handed down by the Supreme Court and adopted as PTO policy. For example, the rejection failed to consider claim 6 as a whole. The rejection failed to identify the differences between claim 6 and the cited documents. And, the rejection failed to engage in any analysis relating to whether the claimed invention as a whole would have been obvious. That was error. *See Graham v. John Deere Co.*, 383 US 1, 17-18, 148 USPQ 459, 467 (1966); and MPEP §2141 at 2100-115 ("Office policy is to follow *Graham v. John Deere Co.* in the consideration and determination of obviousness under 35 USC §103."); and *Ex Parte Roller*, 2004 WL 45458, *2 (unpublished) (BPAI 2004) ("In rejecting claims under 35 USC §103, it is incumbent upon the Examiner to establish a factual basis to support the legal conclusion of obviousness. In doing so, the Examiner is expected to make the factual determinations set forth in *Graham v. John Deere Co.*, and to provide a reason why one having ordinary skill in the art would have been led to modify the prior art or to combine prior art references to arrive at the claimed invention.") (citations omitted).

The Examiner did not acknowledge the specific temperature and pressure ranges recited in claim 6. The Examiner made no findings with respect to the specific temperature and pressure ranges, if any, disclosed in Higashidate and Nakamura. And, the Examiner made no finding with respect to why one skilled in the art would have believed that the process recited in claim 6, as a whole, would have been obvious in

view of the disclosures of Higashidate alone, or in combination with, Nakamura. For this additional reason, the rejection of claim 6 should be reversed.

The sole argument presented by the Examiner with respect to claim 4, was that it was within the "skill in the art," for one to determine the particular size and shape of the silica gel particles recited in claim 4. (Paper No. 24 at 4). Such a "within the skill of the art standard," however, has been expressly rejected by the Board. *See, e.g., Ex parte Levengood*, 28 USPQ2d at 1302 (that which is within the skill of one in the art is not synonymous with obviousness).

Moreover, because the Examiner carried out the "within the skill of the art" analysis at the wrong point in time – at the time the rejection was written – the rejection must also fail. *Fine*, 5 USPQ2d at 1598. It is simply irrelevant what one who "***is*** familiar with separation techniques" knows. Again, the Examiner failed to conduct the analysis at the time the invention was made. Thus, notwithstanding the application of the wrong standard, the rejection of claim 4 must also fail because the Examiner did not go back in time to conduct the appropriate analysis at the appropriate time.

CONCLUSION

For all of the foregoing reasons, it respectfully is submitted that the Examiner failed to make out a *prima facie* case of obviousness and hence the rejection of claims 1-6 should be reversed.

Respectfully submitted,

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APPENDIX

1. A process for the isolation of vitamin D_3 or previtamin D_3 from a mixture containing vitamin D_3 or previtamin D_3, which process comprises separating the vitamin D_3 or previtamin D_3 by a normal phase column chromatographic technique with back-pressure regulation, wherein a mobile phase of the chromatography comprises supercritical carbon dioxide.

2. A process according to claim 1, wherein the mobile phase further comprises a modifier.

3. A process according to claim 1, wherein a silica gel is used as the stationary phase.

4. A process according to claim 1, wherein the silica gel is in the form of homogeneously packed, spherical particles having a particles size of about 5 to 25 μm.

5. A process according to claim 1, wherein a reaction mixture synthetically produced by irradiation is used as a mixture of vitamin D_3 isomers.

6. A process according to claim 1, which is carried out in the temperature range from about 30°C to about 60°C and in the pressure range from about 7.0 to about 15.0 MPa.